PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: J. Timothy GREENAMYRE, et al
Serial No.: 09/148,973 Group No.: 1627
Filed: September 4, 1998 Examiner.: Maurice Garcia Baker
For: METHODS OF ADMINISTERING AN AMPA RECEPTOR ANTAGONIST TO TREAT DYSKINESIAS ASSOCIATED WITH DOPAMINE AGONIST THERAPY

Attorney Docket No.: U 946765-7

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Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICIAL ACTION OF FEBRUARY 25, 2003

The Official Action of February 25, 2003 has been carefully considered and reconsideration of the application in view of the present submission is respectfully requested.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231

CLIFFORD J. MASS
(Type or print name of person mailing paper)

Date: July 22, 2003

(Signature of person mailing paper)

The Examiner has maintained the rejections of claims 1-3 and 5-7 under 35 USC 103(a) for alleged unpatentability over Arnold et al in view of Adams et al. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to combine reference teachings; (2) there must be a **reasonable expectation of success**; and (3) the combination of references must teach or suggest all of the claim limitations (see MPEP Section 706.02(j)). The Examiner contends that the claimed method for treating dyskinesia associated with dopamine agonist therapy would have been *prima facie* obvious from a combination of Arnold et al and Adams et al, because (a) Arnold et al allegedly teach that blocking AMPA receptors is an effective way to treat neurological disorders such as dyskinesias; (b) Adams et al teach that dyskinesia is one of the "most common and troublesome effects of L-dopa"; and (c) the references allegedly provide a motivation for their combination. Even assuming for the sake of argument that the references provide a motivation for their combination, the references still would fail to set forth a *prima facie* case of obviousness because there would not have been even a reasonable expectation of success in practicing the claimed method.

In this respect, Applicants et al first respectfully note that the Examiner's primary reference, Adams et al, when viewed in a light most favorable to the Examiner's position, teaches that blocking AMPA receptors is an effective way to treat neurological disorders such as **tardive** dyskinesia, i.e. dyskinesia mainly associated with antipsychopathic drugs that act as an **antagonist** to dopamine receptors (see, e.g., US Patent 5,712,282 at column 1, lines 18-24). The primary

reference does not show or suggest that blocking AMPA receptors would be an effective way to treat any other dyskinesia, and *a fortiori* does not show or suggest the treatment of dyskinesia associated with dopamine **agonist** therapy. Indeed, the reference is very specific in naming tardive dyskinesia and tardive dyskinesia only. In this respect, it must be emphasized that certain dyskinesias, such as tardive dyskinesia, are classified by their etiology and the very fact of such classification would mitigate against a generalization with respect to treatment of a dyskinesia with a different etiology, as next discussed.

Tardive dyskinesia (TD) is one in a broad category of movement disorders thought to involve pathology of the basal ganglia, which category also includes Parkinson's disease, drug-induced parkinsonism, the choreas, ballism, the athetoses, the dystonias including tardive (and other) dystonias, akathisia, Huntington's disease, and several degenerative and atrophic syndromes, (see US Patent 5,670,539 at column 5, line 61-column 6, line 7). As of the filing date of the application, it was poorly understood how basal ganglia control movements, and it was thought that the manifestation of abnormal movement disorders, such as TD, at a minimum involved several neurotransmitter systems, and that vulnerability to such disorders might be multifaceted (US Patent 5,670,539 at column 7, lines 3-7). Significantly one facet of this vulnerability was thought to involve an imbalance in serotonin-dopamine interactions in the brain (US Patent 5,670,539 at column 8, line 60-column 9, line 5).

In view of the diverse and multifaceted nature of the movement disorders and the apparent involvement of a number of different neurotransmitter systems, including neurotransmitter system(s) involving dopamine, those of skill in the art could not have

predicted that a dyskinesia associated with a dopamine **agonist** therapy could be effectively treated in the same manner as a dyskinesia associated with a dopamine **antagonistic** therapy. In particular, those of skill in the art could not have known what effects administering an AMPA receptor antagonist could have on the seratonin-dopamine interactions in patients treated with L-dopa and whether such effects would, for example, offset or exacerbate the effects caused by the dopamine agonist therapy. (As discussed in Applicants' response filed October 28, 2002 in the paragraph bridging pages 2-3, a previously cited reference to Klockgether et al demonstrated that an AMPA receptor antagonist potentiates the effects of a dopamine agonist in animal models of bradykinesia.)

The secondary reference does not supplement the primary reference with respect to the establishment of a reasonable expectation of success, and in fact has apparently been cited simply to show that dyskinesia associated with dopamine agonist therapy is a common and troublesome problem whereby to provide an alleged motivation for combining the references. What is missing is a reference that would provide a reasonable expectation that using the AMPA receptor antagonists of the primary reference would enable an effective treatment of dyskinesia associated with dopamine agonist therapy. In the absence of a reference establishing a reasonable expectation of success in treating a dyskinesia with this etiology, it is respectfully submitted that the Examiner has not set forth even a *prima facie* case of obviousness for the invention as claimed.

The Examiner has also maintained the rejections of claims 1-3 and 5-7 under 35 USC 103(a) for alleged unpatentability over Stella et al in view of Arnold et al and

further in view of Adams et al. Applicants respectfully traverse this rejection as well.

As is the case with the rejection discussed above, it is respectfully submitted that the references in this rejection do not set forth even a *prima facie* case of alleged obviousness due at least to the absence of any reference that would provide even a reasonable expectation of success in practicing the claimed method. The only additional reference in the present rejection, Stella (Papa and Chase), relates to the use of antagonists to a different type of glutamate receptor from the AMPA receptor. However, as discussed in detail in Applicants' response filed October 28, 2002, the reports in the literature prior to the application filing date showed that the respective AMPA and NMDA receptors have clearly distinct physiologies (Seeburg, 1993; Dingledine et al., 1999) and that AMPA and NMDA receptor antagonists have very different physiological effects (Browne and McCulloch, 1994; Durmuller et al., 1994; Sheardown et al., 1993; Papa et al., 1993). This being the case, there would have been no basis (absent the hindsight provided by the present specification) for one of skill in the art to expect that the use of an antagonist that blocks an AMPA receptor would have a similar effect to the use of an antagonist that blocks an NMDA receptor.

The Examiner has correctly noted that the test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art and that all teachings in the relevant prior art must be considered. However, as discussed above, none of the cited references, whether considered alone or in combination, provides any suggestion of success in the treatment of a dyskinesia associated with dopamine agonist therapy by blocking AMPA receptors. In particular, the Arnold et al reference, which is cited by the Examiner as allegedly

showing that blocking AMPA receptors is an effective way to treat neurological disorders, such as "dyskinesias", in fact at most teaches that such blocking can be used to treat **tardive** dyskinesia, i.e. a dyskinesia categorized by its etiology (see discussion above). There is nothing in this or any other of the cited references that would suggest that blocking AMPA receptors would be an effective way to treat a dyskinesia with a completely different etiology, i.e., a dyskinesia associated with dopamine agonist therapy as claimed. In the absence of such teaching, it is respectfully submitted that the cited references do not set forth even a *prima facie* case of alleged obviousness for the invention as claimed.

In view of the above, it is respectfully submitted that the rejections of record should be withdrawn and that the application is in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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